AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claim:

Claims 1-3. (Cancelled)

4. (Currently Amended) A polyarginine containing crystal of human growth hormone (hGH), wherein said hGH is selected from the group consisting of:

(a) the 191 amino acid sequence of native hGH; and

(b) the 192 amino acid sequence of said 191 amino acid sequence of native hGH additionally containing an N-terminal methionine ~~or a polyarginine crystal of a human growth hormone derivative~~.

Claims 5-6. (Cancelled)

7. (Currently Amended) ~~The crystal according to claim 4,~~A polyarginine containing crystal of human growth hormone (hGH), wherein said hGH is selected from the group consisting of:

(a) the 191 amino acid sequence of native hGH; and

(b) the 192 amino acid sequence of said 191 amino acid sequence of native hGH additionally containing an N-terminal methionine;

wherein the crystal is characterized by a release profile such that a single administration of said crystal to a mammal provides an *in vivo* human growth hormone (hGH) serum concentration profile in said mammal having a $T^{90\%}$ value higher than that provided by a single administration of the same amount of soluble human growth hormone.

8. (Currently Amended) ~~The crystal according to claim 4,~~ A polyarginine containing crystal of human growth hormone (hGH), wherein said hGH is selected from the group consisting of:

(a) the 191 amino acid sequence of native hGH; and

(b) the 192 amino acid sequence of said 191 amino acid sequence of native hGH additionally containing an N-terminal methionine;

wherein the crystal is characterized by an insulin growth factor-1 (IGF-1) serum elevation profile such that a single administration of said crystal to a mammal provides an *in vivo* IGF-1 serum elevation over baseline IGF-1 level in said mammal at similar levels compared to those provided by the same amount of soluble human growth hormone (hGH) administered in more than one administration.

9. (Currently Amended) ~~The crystal according to claim 4,~~ A polyarginine containing crystal of human growth hormone (hGH), wherein said hGH is selected from the group consisting of:

(a) the 191 amino acid sequence of native hGH; and

(b) the 192 amino acid sequence of said 191 amino acid sequence of native hGH additionally containing an N-terminal methionine;

wherein the crystal is characterized by a bioavailability such that a single administration of said crystal has a relative bioavailability of at least 50% or more, as compared to that of an identical dose of soluble human growth hormone (hGH)) delivered via the same administrative route, wherein said bioavailability is measured by area under curve (AUC) of total *in vivo* hGH serum concentration for said soluble hGH and said hGH crystal.

10. (Original) The crystal according to claim 7 or 8, wherein said mammal is a human.

Claims 11-16. (Cancelled)

17. (Currently Amended) A composition comprising the polyarginine containing crystals according to claim 4, 7, 8 or 9, ~~crystals of human growth hormone (hGH) or crystals of a human growth hormone derivative~~ and an excipient~~, wherein said crystals are polyarginine crystals of human growth hormone or polyarginine crystals of a human growth hormone derivative~~.

18. (Previously Presented) The composition according to claim 17, wherein said crystals and said excipient are present in said composition at a molar ratio of human growth hormone (hGH):excipient of 1:10 to 1:0.125.

19. (Original) The composition according to claim 17, wherein said excipient is selected from the group consisting of: amino acids, salts, alcohols, carbohydrates, proteins, lipids, surfactants, polymers, polyamino acids and mixtures thereof.

20. (Original) The composition according to claim 19, wherein said excipient is selected from the group consisting of: protamine, polyvinylalcohol, cyclodextrins, dextrans, calcium gluconate, polyamino acids, polyethylene glycol, dendrimers, polyorthinine, polyethyleneimine, chitosan and mixtures thereof.

21. (Original) The composition according to claim 20, wherein said excipient is selected from the group consisting of: protamine, polyarginine, polyethylene glycol and mixtures thereof.

22. (Currently Amended) The composition according to claim 17, wherein the concentration of human growth hormone (hGH) ~~or human growth hormone derivative~~ in said composition is between 0.1 and 100 mg/ml.

23. (Withdrawn) A method for treating a mammal having a disorder associated with human growth hormone deficiency or which is ameliorated by treatment with human growth hormone, comprising the step of administering to said mammal a

therapeutically effective amount of a crystal according to any one of claims 1, 2, 3 or 4, or composition according to claim 17.

24. (Withdrawn) A method for inducing weight gain in a mammal, comprising the step of administering to said mammal a therapeutically effective amount of a crystal according to any one of claims 1, 2, 3 or 4, or a composition according to claim 17.

25. (Withdrawn) The method according to claim 24, wherein said mammal is a hypophysectomized rat and the weight gain induced in said rat is between 5% and about 40% following administration of said crystals by injection once a week.

26. (Withdrawn) The method according to claim 23, wherein said disorder is selected from the group consisting of: adult growth hormone deficiency, pediatric growth hormone deficiency, Prader-Willi syndrome, Turner syndrome, short bowel syndrome, chronic renal insufficiency, idiopathic short stature, dwarfism, hypopituitary dwarfism, bone regeneration, female infertility, intrauterine growth retardation, AIDS-related cachexia, Crohn's disease and burns.

27. (Withdrawn) The method according to claim 26, wherein said disorder is pediatric growth hormone deficiency and said method results in annualized growth velocity in said mammal of between about 7 and about 11 cm.

28. (Withdrawn) The method according to claim 23 or 24, wherein said crystal or composition is administered to said mammal by oral route, parenteral route, subcutaneous route or intramuscular route.

29. (Withdrawn) The method according to claim 28, wherein said crystal or composition is administered to said mammal by subcutaneous route using a needle having a gauge greater than or equal to 27.

30. (Withdrawn) The method according to claim 23 or 24, wherein said crystal or composition is administered to said mammal by needle-free injection or meta dose infusion pump.

31. (Withdrawn) The method according to claim 23 or 24, wherein said crystal or composition is administered to said mammal by a time regimen selected from the group consisting of:

(a) about once every three days;

(b) about once a week;

(c) about once every two weeks; and

(d) about once every month.

32. (Withdrawn) The method according to claim 23 or 24, wherein said mammal is a human.

33. (Withdrawn) A method for producing calcium crystals, monovalent cation crystals, protamine crystals or polyarginine crystals of human growth hormone or a human growth hormone derivative, comprising the steps of:

(a) mixing a solution of human growth hormone or a human growth hormone derivative with a crystallization solution, said crystallization solution comprising a calcium salt or a monovalent cation salt and an ionic polymer, wherein said ionic polymer is protamine or polyarginine; and

(b) incubating said crystallization solution for greater than about 12 hours at a temperature between about 4°C and about 37°C, until calcium crystals, monovalent cation crystals, protamine crystals or polyarginine crystals of human growth hormone or a human growth hormone derivative are produced.

34. (Withdrawn) The method according to claim 33, wherein said ionic polymer is polylysine.

35. (Withdrawn) The method according to claim 33, wherein said ionic polymer is a mixture of any two or more of protamine, polyarginine and polylysine.

36. (Withdrawn) A method for producing calcium crystals or monovalent cation crystals of human growth hormone or a human growth hormone derivative, comprising the steps of:

(a) mixing a solution of human growth hormone or a human growth hormone derivative with a crystallization buffer to produce a crystallization solution;

(b) adding deionized water to said crystallization solution;

(c) adding a precipitant to said crystallization solution;

(d) adding a calcium salt or a monovalent cation salt to said crystallization solution;

(e) incubating said crystallization solution for between about 2 and about 168 hours at a temperature between about 10°C and about 40°C, until calcium crystals or monovalent cation crystals of human growth hormone or a human growth hormone derivative are formed; and

(f) adding an ionic polymer or an ionic small molecule to said calcium crystals or monovalent cation crystals of human growth hormone or a human growth hormone derivative.

37. (Withdrawn) A method for producing calcium crystals or monovalent cation crystals of human growth hormone or a human growth hormone derivative, comprising the steps of:

(a) mixing a solution of human growth hormone or a human growth hormone derivative with a crystallization buffer to produce a crystallization solution;

(b) adding deionized water to said crystallization solution;

(c) adding an ionic small molecule or an ionic polymer to said crystallization solution;

(d) adding a calcium salt or monovalent cation salt to said crystallization solution; and

(e) incubating said crystallization solution for between about 2 and about 168 hours at a temperature between about 10°C and about 40°C, until calcium crystals or monovalent cation crystals of human growth hormone or a human growth hormone derivative are formed.

38. (Withdrawn) The method according to claim 37, wherein, following step (b) and prior to step (c), said method comprises the step of: adding a precipitant to said crystallization solution.

39. (Withdrawn) The method according to any one of claims 33, 36 or 37, wherein said calcium salt is selected from the group consisting of: calcium acetate, calcium chloride, calcium gluconate and calcium sulfate.

40. (Withdrawn) The method according to claim 39, wherein said calcium salt is calcium acetate.

41. (Withdrawn) The method according to any one of claims 33, 36 or 37, wherein said monovalent cation is selected from the group consisting of: lithium, sodium, potassium and ammonium.

42. (Withdrawn) The method according to claim 41, wherein said monovalent cation is sodium.

43. (Withdrawn) The method according to any one of claims 33, 36 or 37, wherein said monovalent cation salt is selected from the group consisting of: sodium citrate, sodium phosphate and sodium acetate.

44. (Withdrawn) The method according to claim 43, wherein said monovalent cation salt is sodium acetate.

45. (Withdrawn) The method according to claim 33, wherein said crystallization solution further comprises a pH buffer.

46 (Withdrawn) The method according to claim 45, wherein said pH buffer is a buffer selected from the group consisting of: Tris, HEPES, acetate, phosphate, citrate, borate, imidazole and glycine.

47. (Withdrawn) The method according to claim 36 or 38, wherein said precipitant is a non-ionic small molecule or a non-ionic polymer.

48. (Withdrawn) The method according to claim 47, wherein said non-ionic polymer is selected from the group consisting of: polyethylene glycol, polyvinyl alcohol and mixtures thereof.

49. (Withdrawn) The method according to claim 48, wherein said polyethylene glycol is present in said crystallization solution at a concentration between about 0.5% and about 20% (w/v).

50. (Withdrawn) The method according to claim 36 or 38, wherein said precipitant is selected from the group consisting of: amino acids, peptides, polyamino acids and mixtures thereof.

51. (Withdrawn) The method according to any one of claims 33, 36 or 37, wherein said human growth hormone or human growth hormone derivative is present in said crystallization solution at a concentration selected from the group consisting of:

(a) a concentration between about 1 mg/ml and about 1,000 mg/ml;

(b) a concentration between about 2 mg/ml and about 50 mg/ml; and

(c) a concentration between about 10 mg/ml and about 25 mg/ml.

52. (Withdrawn) The method according to any one of claims 33, 36 or 37, wherein said calcium salt or said monovalent cation salt is present in said crystallization solution at a concentration selected from the group consisting of:

(a) a concentration between about 0.01 and about 1 M; and

(b) a concentration between about 25 and about 205 mM.

53. (Withdrawn) The method according to any one of claims 33, 36 or 37, wherein said crystallization solution is incubated for a time and a temperature selected for the group consisting of:

(a) between about 0.25 day and about two days at a temperature of about 33°C;

(b) between about 0.25 day and about two days at a temperature of about 25°C; and

(c) between about 0.25 day and about two days at a temperature of about 15°C.

54. (Withdrawn) The method according to claim 36 or 37, wherein said ionic small molecule is selected from the group consisting of: amino acids, peptides and mixtures thereof.

55. (Withdrawn) The method according to claim 36 or 37, wherein said ionic polymer is selected from the group consisting of: protamine, polysaccharides, polyamino acids, polyarginine, polylysine, polyglutamate, dendrimers, polyorthinine, polyethyleneimine, chitosan and mixtures thereof.

56. (Withdrawn) The method according to claim 55, wherein said ionic polymer is protamine or polyarginine.

57. (Withdrawn) The method according to claim 36 or 37, wherein said crystallization buffer is selected from the group consisting of: Tris-HCl buffer, glycine buffer, HEPES buffer, imidazole buffer, Bis-Tris buffer, AMP, AMPD, AMPSO, bicine, Ethanolamine, glyclglycine, TAPS, Taurin, Triane and mixtures thereof.

58. (Withdrawn) The method according to claim 36 or 37, wherein, in step (a) of claim 36 or step (a) of claim 37, said crystallization buffer is present in said crystallization solution at a concentration between about 10 mM and about 800 mM.

59. (Withdrawn) The method according to claim 44, wherein, in step (e) of claim 36 or step (e) of claim 37, said sodium acetate is present in said solution at a concentration selected from the group consisting of:

(a) a concentration between about 0.5 mM and about 800 mM; and

(b) a concentration between about 100 mM and about 500 mM.

60. (Currently Amended) The polyarginine containing crystal according to claim 4, 7, 8 or 9, wherein the polyarginine is co-crystallized with the human growth hormone (hGH) ~~or the human growth hormone derivative~~.

61. (Currently Amended) The polyarginine containing crystal according to claim 4, 7, 8 or 9, wherein the polyarginine is complexed to crystals of the human growth hormone (hGH) ~~or crystals of the human growth hormone derivative~~.

62. (Currently Amended) ~~A~~The polyarginine containing crystal ~~of human growth hormone or a polyarginine crystal of a human growth hormone derivative~~according to claim 4, 7, 8 or 9, wherein the crystal is produced by co-crystallizing a human growth hormone ~~or a human growth hormone derivative~~ with ~~polyarginine.~~

63. (Currently Amended) ~~A~~The polyarginine containing crystal ~~of human growth hormone or a polyarginine crystal of a human growth hormone derivative~~ according to claim 4, 7, 8 or 9, wherein the crystal is produced by:

(a) crystallizing ~~a~~the human growth hormone ~~or a human growth hormone derivative~~, and

(b) complexing polyarginine to the crystallized human growth hormone ~~or human growth hormone derivative crystals~~.

64. (Currently Amended) The polyarginine containing crystal according to any one of claims 4, 7, 8, 9 and 60 to 63, further comprising a cation.

65. (Currently Amended) A pharmaceutical composition comprising the polyarginine containing crystal of human growth hormone ~~or the polyarginine crystal of a human growth hormone derivative~~ of claims 4, 7, 8, 9, 62, 63 or 64.